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(54) Title: FENTANYL CONTAINING AEROSOL COMPOSITIONS

(57) Abstract

Fentanyl and physiologically acceptable derivatives thereof dissolved or dispersed in an aerosol propellant to form an aerosol formulation for administration by inhalation.

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Fentanyl containing aerosol compositions.

This invention relates to analgesic formulations and in particular to analgesic formulations comprising fentanyl suitable for administration by inhalation.

Narcotic analgesics are used to relieve moderate to severe pain, particularly of a visceral origin. The narcotic analgesics are generally administered by sub-cutaneous, intra-muscular or intravenous injection, or orally in the form of elixirs, tablets (optionally sublingual) and capsules, or by rectal administration in the form of suppositories. In the case of patients who are hospitalised narcotic analgesics are often administered in the form of saline drips.

Since the metered dose pressurised inhaler was introduced in the mid 1950's, inhalation has become the most widely used route for delivering bronchodilator drugs and steroids to the airways of asthmatic patients. Compared with oral administration of bronchodilators, inhalation offers a rapid onset of action and a low instance of systemic side effects. More recently, inhalation from a pressurised inhaler has been a route selected for the administration of other drugs, e.g., ergotamine, which are not primarily concerned with treatment of a bronchial malady.

Various publications, e.g., British Patents Nos. 830426, 837465, 994734 and 2125426; European Patent Nos. 0162239 and WO86/04233 which relate to self-propelling pharmaceutical compositions for administration from pressurised inhalers disclose the possibility of employing an analgesic such as morphine, diamorphine and buprenorphine hydrochloride in such formulations although there is no disclosure of any specific formulations containing such analgesics nor any indication of their efficiency when administered by inhalation.

It has now been found that morphine and diamorphine hydrochloride are considerably less potent when administered by inhalation using self-propelling aerosol compositions than might have been expected from the known intravenous dosing data. It has also been found that fentanyl and in particular fentanyl citrate exhibits a potent, quick acting effect when administered by inhalation from a self-propelling aerosol formulation.

Therefore according to the present invention there is provided an aerosol formulation comprising fentanyl or a physiologically acceptable derivative thereof dispersed or dissolved in an aerosol propellant.

The invention also provides a pressurised aerosol inhaler comprising a container, containing an aerosol formulation as defined above, and a valve capable of dispensing metered doses of the formulation. The pressurised aerosol preferably incorporates the means to control the dosing frequency from the valve such that not more than a predetermined maximum number of doses may be dispensed within a set period of time. Such a pressurised inhaler allows the maximum dosage frequency available to the patient to be pre-set, whilst insuring the patient cannot receive an overdose. The inhaler provides the benefits of on-demand dosing for the patient with dosage control, and may be used both in hospitals and homes without requiring medical personnel to administer each dose.

The formulations used in the invention contain fentanyl or a derivative thereof either in solution or suspension in the aerosol propellant system, optionally in the presence of a cosolvent. The solvent for fentanyl will generally be present in an amount in the range 5 to 25% by weight of the composition. The compositions may additionally comprise one or more surface active agents, for example oleic acids, complex esters and ester-ethers, e.g., sorbitan trioleate, Span 85, lecithins such as Epikuron 200, and fluorinated surfactants. The weight ratio of surface active agent to fentanyl is generally in

the range 1 : 100 to 10 : 1. The concentration of fentanyl will generally be within the range 0.05 to 5.00%, preferably 0.1 to 1.0%, by weight based on the total composition.

A wide range of propellants may be used in the aerosol formulations of the invention including:

Propellant 11	trichloromonofluoromethane
Propellant 12	dichlorodifluoromethane
Propellant 13	monochlorotrifluoromethane
Propellant 21	dichloromonofluoromethane
Propellant 22	monochlorodifluoromethane
Propellant 113	trichlorotrifluoroethane
Propellant 114	dichlorotetrafluoroethane
Propellant 115	monochloropentafluoroethane
Propellant 134a	1,1,1,2-tetrafluoroethane
Propellant 500	azeotrope of dichlorodifluoromethane and 1,1-difluoroethane

In addition to chlorofluorocarbon aerosol propellants the formulations may contain other propellants, for example, DME (dimethylether), hydrocarbons and perfluorocarbons.

One preferred propellant system is disclosed in our co-pending British Patent Application No. 8828477.3 and comprises 1,1,1,2-tetrafluoroethane, a surface active agent and at least one compound having a higher polarity than 1,1,1,2-tetrafluoroethane. Suitable compounds having a higher polarity than 1,1,1,2-tetrafluoroethane include alcohols, such as ethyl alcohol, isopropyl alcohol, propylene glycol, hydrocarbons such as propane, butane, isobutane, pentane, isopentane, neopentane, and mixtures thereof. The 1,1,1,2-tetrafluoroethane preferably comprises at least 50% by weight of the formulation, preferably from 60 to 95% by weight of the formulation. The weight ratio of 1,1,1,2-tetrafluoroethane to the compound of higher polarity is generally in the range 50 : 50 to 90: 1, preferably 70 : 30 to 98 : 2, more preferably 85 : 15 to 95 : 5.

In an alternative system the fentanyl or derivative thereof in the form of a finely divided solid is coated with a dry coating of a perfluorinated surface-active dispersing agent and thereafter mixed with an aerosol propellant. Such systems are disclosed generally in U.S. Patent No. 4,352,789. The preferred propellant for such formulation is 1,1,1,2-tetrafluoroethane, preferably with an adjuvant having a polarity equal to or lower than the polarity of 1,1,1,2-tetrafluoroethane.

Suitable adjuvants having a polarity equal to or lower than Propellant 134a include perfluorinated organic compounds such as perfluorinated alkanes and cycloalkanes. Specific examples of adjuvants include perfluoropropane, perfluorobutane, perfluorocyclobutane, perfluoropentane, perfluorohexane, perfluorotributylamine, perfluoromethylcyclohexane and perfluorodecalin. Such compositions generally comprise from 0.001 to 20% by weight of finely-divided solid fentanyl coated with a perfluorinated surface-active dispersing agent which constitutes at least 0.001%, normally 0.001 to 50%, preferably 0.001 to 20% by weight of the coated solid material, and suspended in an aerosol propellant comprising 1,1,1,2-tetrafluoroethane and an adjuvant having a polarity equal to or lower than that of 1,1,1,2-tetrafluoroethane.

The perfluorinated surface-active dispersing agents (hereinafter referred to as "perfluorinated surfactants" or "surfactants") are substantially insoluble in the propellant. This insolubility is due to the relatively ionic character of one end of the surfactant molecule. This ionic group is compatible with the solid powdered material and enables the surfactant to wet the solid material. Although the perfluorinated surfactant is insoluble in the propellant, when coated on the solid material, the outermost perfluorinated groups of the surfactant allow the solid coated material to be dispersed in the propellant due to the compatibility between the perfluorinated groups and the propellant.

Perfluorinated surfactants most useful in the compositions of the present invention include perfluorinated alcohol phosphate esters and their salts; perfluorinated sulfonamide alcohol phosphate esters and their salts; perfluorinated alkyl sulfonamide alkylene quaternary ammonium salts; N,N-(carboxyl-substituted lower alkyl) perfluorinated alkyl sulfonamides; and mixtures thereof. By "perfluorinated" it is meant that the surfactant contains at least one perfluorinated alkyl group. Particularly preferred perfluorinated alcohol phosphate esters are the free acids of the diethanolamine salts of mono- and bis(1H,1H,2H,2H-perfluoroalkyl) phosphates. The phosphate salts, available under the trade name "Zonyl RP" from E. I Dupont de Nemours and Company, Wilmington, Del., are converted to the corresponding free acids.

Preferred perfluorinated sulfonamide alcohol phosphate esters are described in U.S. Patent No. 3,094,547, and have the general formula:

$$[R_fSO_2N(R)R'O]_mP(OH)_{3-m}$$

in which;

R is hydrogen or an alkyl group having from 1 to about 12, preferably from 1 to 6, carbon atoms; R' is an alkylene bridging group containing 2 to about 12 carbon atoms, preferably from 2 to 8 carbon atoms; R_f is a perfluorinated radical selected from perfluoroaliphatic groups of general formula C_nF_{2n+1} or perfluorocycloaliphatic groups of general formula C_nF_{2n-1} in which; n is an integer from 1 to 18, preferably from 6 to 12, and m is an integer from 1 to 3.

Although the mono-, di- and triesters are useful, the diester is most readily available commercially. Particularly preferred perfluorinated sulfanomide alcohol phosphate esters and salts of these include perfluoro-n-octyl-N-ethylsulfonamidoethyl phosphate, bis(perfluoro-n-octyl-N-ethylsulfonamidoethyl)phosphate, the ammonium

salt of bis(perfluoro-n-octyl-N-ethyl-sulfonamidoethyl) phosphate, bis(perfluorodecyl-N-ethylsulfonamidoethyl) phosphate and bis(perfluorohexyl-N-ethylsulfonamidoethyl) phosphate. The above named preferred surfactants are of particular use in medicinal aerosol compositions due to their non-irritating and non-toxic nature.

The preferred perfluorinated alkyl sulfonamide alkylene quaternary ammonium salt for use in the preparation of aerosol medicaments according to the present invention is N,N-dimethyl-N-decyl-N-(perfluoro-n-octylsulfonamidopropyl)ammonium bromide.

A preferred N,N-bis(carboxyl-substituted lower alkyl)perfluorinated alkyl sulfonamide for use with medicaments in aerosol compositions of the present invention is N,N-bis(4-carboxyl-n-butylperfluoro-n-octylsulfonamide).

The perfluorinated surfactant constitutes at least 0.001% and generally up to 50%, usually up to 20%, desirably between 0.1 and 5%, and preferably, for medicinal purposes, between 0.1 and 1% by weight of the solid material to be suspended. However, the minimum amount of perfluorinated surfactant required is dependent upon the concentration of solid material present. For best results, the concentration of perfluorinated surface-active agent is kept at a minimum as it may tend to increase the droplet size of the aerosol particles.

The particle size of the powder should desirably be no greater than 100μm diameter, since larger particles may tend to agglomerate, separate from the suspension and may clog the valve or orifice of the container. Preferably the particle size should be less than 25μm in diameter. Desirably the particle size of the finely-divided solid powder should for physiological reasons be less than 25μm and preferably less than about 10μm in diameter. The particle size of the powder for inhalation therapy should preferably be in the range 2 to 10 microns.

The finely-divided solid material may constitute up to about 20% by weight of the total composition. Desirably it shall constitute up to 10%, generally up to 5% and preferably up to 3%, by weight of the total composition. The minimum concentration of the solid material is governed by its specific activity and in the case of highly active material can be as low as 0.001% by weight of the total composition although a concentration of 0.01% is preferred.

It is also possible to coat finely divided solid fentanyl or derivatives thereof with non-perfluorinated surface-active agents in similar manner and thereafter mix with a wide range of aerosol propellants. Propellant 134a is preferred because of its ozone friendly properties.

Other propellant systems which may be employed include mixtures of aerosol propellants. General concentration ranges for specific propellants which may be employed in admixtures are as follows:

Propellant 11 : 15 to 25% by weight
Propellant 12 : 50 to 90% by weight
Propellant 22 : 5 to 50% by weight

The aerosol formulations of the invention are preferably used in a pressurised aerosol inhaler comprising a container and a valve capable of dispensing doses of the formulation, in which the inhaler additionally comprises means to control the dosing frequency from the valve.

The control means preferably comprises an electronic timing device associated with means to prevent actuation of the valve of the pressurised aerosol inhaler such that the inhaler may be disabled until the end of a controlled period of time during which a pre-set maximum number of doses have been dispensed. The electronic time control of the dosing frequency can take either of the following forms:

(i) The patient can take from 1 to 'N' doses at the start of the control period 'T'. The clock starts when the first dose is dispensed; the patient then has a shorter period 't' to take further doses up to 'N'. The device then locks out for the remainder of the control period 'T'.

(ii) The patient can take up to 'N' doses during the whole of the control period. The clock starts at the first dose in a new control period.

Option (ii) is the preferred dosage-control mode for most situations. The control period, 'T', and the maximum number of doses 'N' can be either factory pre-set or adjustable by medical or nursing staff. The inhaler device may have provision for internal adjustment of these control parameters. Alternatively, the controls may be positioned externally using one-way rotary switches which allow only increase of time 'T' and reduction of the maximum number of doses 'N' to prevent overdosage. The parameters may be set to ensure a sufficient time has elapsed for a dose to take effect before the patient may take a further dose.

A further control feature which may be incorporated in the device is a locking mechanism designed to effect permanent disablement of the device after the label-claim number of doses has been dispensed, thus allowing precise control of the number of doses available from each aerosol container.

A further feature which may be incorporated into the inhaler device is a liquid crystal display which may display a variety of information, for example:

(a) the balance of the label-claim number of doses remaining in the aerosol canister,

(b) the time remaining in the current control period, and,

(c) the number of available doses remaining in the current control period.

Suitable inhaler devices are shown in the accompanying drawings in which:

Figure 1 represents a diagram of an inhaler, and,

Figure 2 represents a block diagram of an electrical circuit for use in the inhaler of Figure 1.

Referring to Figures 1 and 3 of the accompanying drawings, the inhalation devices comprise a housing 2 accommodating an aerosol container 4 having a dispensing valve 6. The aerosol container 4 is mounted vertically with the outlet valve 6 positioned within a nozzle block 8. The housing 2 has a mouthpiece 10 which may be adapted by the provision of a nasal adaptor if the medicament is to be administered via the nose. In use, the patient inhales via the mouthpiece 10, initiating movement of the container relative to the valve, causing a dose of medicament to be fired from the valve, through the nozzle block, into the mouthpiece, and thence into the lungs as the patient inhales.

In the inhaler shown in Figure 1, the start of inhalation is sensed by a precision-moulded triggering mechanism which responds to an inhalation flow rate of about 30 litres/minute. The triggering mechanism comprises a vane 20 associated with a locking device acting on the nozzle block 8, allowing actuation of the aerosol device only during inhalation. Examples of such arrangements are disclosed in European Patent No. 0147028B. Force is first applied to the aerosol container by the manual raising of cocking lever 22. However, when the device is locked-out by the control means the cocking force will not facilitate actuation of the valve since movement of the vane of the triggering mechanism is blocked by lever 24.

When doses are available to the patient, the control means causes operation of the solenoid 26, causing lever 28 to be pushed forwards and its hooked end to engage within an aperture in lever 24. When cocking lever 22 is then raised, levers 28 and 24 are also raised, so freeing the triggering mechanism for operation. Inhalation will

then move the vane, freeing the nozzle block and allowing the cocking force to move the container relative to the valve, thereby firing the aerosol valve and delivering a dose of medicament.

The electronic circuitry is illustrated in diagrammatical form in Figure 2 and comprises an integrated circuit incorporating a clock regulated by a separate quartz crystal oscillator. The bi-stable d.c. solenoid is controlled via a power switch comprising field effect transistors (F.E.T's). The circuit includes a control switch for selecting the control period 'T', the dosage period 't' and the number of doses 'N'. A liquid crystal display is provided to display one or more types of information defined herein before. The electronic circuitry may readily be reduced to a chip and printed circuit board for accommodation within the device as shown at 13. A battery 15 provides the necessary power. The liquid crystal display may be positioned at any suitable place on the housing.

The entire inhalation device may be compacted and the outer dimensions of the housing may be of the order of 90 mm x 60 mm x 30 mm.

The inhaler may be provided in either a disposable or re-usable form. In the former case the device is completely sealed to prevent access to the aerosol canister. In the latter, it is openable but has a locking mechanism to prevent unauthorised opening. This lock may be either mechanical or take the form of a code-operated electronic lock integrated with the device's electronic circuitry.

The invention will now be illustrated by the following examples.

The fentanyl citrate employed in the Examples contained 64% of the anhydrous base.

Example 1

The following formulations were prepared:

	g/can		g/can	
Fentanyl citrate	0.0031		0.0031	
Span 85	0.0069	(0.1%)	0.0343	(0.5%)
Ethanol (21%w/w)	1.4417		1.4143	
Propellant 12	5.4183		5.4183	
Total	6.87		6.87	
Fentanyl citrate	0.075		0.075	
Span 85	0.658		-	
Epikuron 200	-		0.600	
Propellant 11	7.504		7.504	
Propellant 12	24.714		24.773	
Total	32.951		32.952	

All formulations were filled into glass bottles equipped with non-metering valves.
The formulation containing Epikuron 200 formed a solution.

Example 2

The following suspension formulations were prepared:

	0.5%Span	0.4%Span	0.2%Span	0.1%Span
	g/can	g/can	g/can	g/can
Fentanyl citrate	0.0748	0.0748	0.0748	0.0748
Span 85	0.1648	0.1318	0.0659	0.0330
Propellant 11	7.9998	8.0314	8.0973	8.1302
Propellant 12	24.7140	24.7140	24.7140	24.7140
Total	32.9534	32.952	32.952	32.952

The formulations were filled into glass bottles fitted with non-metering valves. Suspension formulations having a high Span content exhibited a reduced tendency to agglomerate compared with formulations having a lower Span content.

Example 3

The following suspension formulation was prepared:

	g/can
Fentanyl citrate	0.0187
Span 85	0.0412
Propellant 11	1.9996
Propellant 12	6.1785
Total	8.2380

The formulation was filled into 5ml plain aluminium vials fitted with 50 µl valves using a 2 stage pressure fitting in which the non-volatile components were admixed and introduced into the vial, the valve crimped in place and the volatile propellant introduced into the vial through the valve under pressure.

Dosage can be varied by varying the valve size as follows:

Valve Size	Dose Per Shot
25µl	50µg
50µl	100µg
63µl	126µg
100µl	200µg

Example 4

Formulations were calculated for a delivery of 100µg of base per shot when a 50µl valve was fitted, and for a fill weight of 16g. The suspensions were filled into polyethylene terephthalate bottles to allow the appearance of the gross formulation to be studied. All units were prepared by two-stage pressure filling.

The following stable suspensions contained Propellant 134a and ethanol in a weight ratio of 90 : 10.

0.1% w/w Span 85

	mg/ml
Fentanyl citrate	3.1250
Span 85	1.1610
Ethanol	115.6714
Propellant 134a	1041.0426
Total	1161.0000

0.3% w/w Span 85

	mg/ml
Fentanyl citrate	3.1250
Span 85	3.4830
Ethanol	115.4392
Propellant 134a	1038.9528
Total	1161.0000

0.5% w/w Span 85

	mg/ml
Fentanyl citrate	3.1250
Span 85	5.8050
Ethanol	115.2070
Propellant 134a	1036.8630
Total	1161.0000

0.01% w/w Span 85

	mg/ml
Fentanyl citrate	3.1250
Span 85	0.1161
Ethanol	115.7759
Propellant 134a	1041.9830
Total	1161.0000

0.02% w/w Span 85

	mg/ml
Fentanyl citrate	3.1250
Span 85	0.2322
Ethanol	115.7643
Propellant 134a	1041.8785
Total	1161.0000

0.05% w/w Span 85

	mg/ml
Fentanyl citrate	3.1250
Span 85	0.5805
Ethanol	115.7294
Propellant 134a	1041.5651
Total	1161.0000

Example 5

The following stable suspensions were prepared as in Example 4 and contained Propellant 134a and n-Pentane in a ratio of 90 : 10.

0.1% w/w Span 85

	mg/ml
Fentanyl citrate	3.1250
Span 85	1.1610
Pentane	115.6714
Propellant 134a	1041.0426
Total	1161.0000

0.3% w/w Span 85

	mg/ml
Fentanyl citrate	3.1250
Span 85	3.4830
Pentane	115.4392
Propellant 134a	1038.9528
Total	1161.0000

0.5% w/w Span 85

	mg/ml
Fentanyl citrate	3.1250
Span 85	5.8050
Pentane	115.2070
Propellant 134a	1036.8630
Total	1161.0000

Example 6

The following suspensions were prepared as in Example 4 and contained Propellant 134a and Propellant 11 in a ration of 95 : 5.

0.1% w/w Span 85

	mg/ml
Fentanyl citrate	3.1250
Span 85	1.1610
Propellant 11	57.8357
Propellant 134a	1098.8783
Total	1161.0000

0.2% w/w Span 85

	mg/ml
Fentanyl citrate	3.1250
Span 85	2.3220
Propellant 11	57.7776
Propellant 134a	1097.7754
Total	1161.0000

Example 7

Fentanyl citrate formulations of the invention were compared with morphine sulphate, morphine base and diamorphine hydrochloride formulations presented as metered-dose inhalation aerosols in various single-dose and repeat-dose experiments in rodent and non-rodent species.

The comparative formulations were as follows.

	g/can
Diamorphine HCI	0.063 (10% drug overage)
Span 85 (20% of drug)	0.013
Propellant 11	1.640
Propellant 12	5.145
Total	6.860

Morphine Sulphate	0.147
Span 85	0.034
Propellant 11	1.534
Propellant 12	5.145
Total	6.860

Morphine base	0.1200
Span 85	0.0412
Propellant 11	1.8983
Propellant 12	6.1785
Total	8.2380

Each formulation was filled into 5ml vials equipped with 50µl dispensing valves.

Rodent Inhalation Exposure Procedure

The system consisted of an aluminium cylindrical chamber of approximately 41.5 litre volume. It was fitted with a flat top which supported an electrically driven mechanism, capable of actuating up to six inverted metered-dose inhaler (MDI) aerosol cans simultaneously. The duration and frequency of operation was controlled by a time switch.

The MDI can nozzles opened directly into the exposure chamber where the administered aerosol dose was mixed and dispersed by a regulated constant supply of clean dry air. An extract duct at the base of the chamber was connected via a filter to a vacuum system. The pressure within the chamber was maintained just below atmospheric pressure.

MDI cans were selected, weighed and inverted in the template of the actuating mechanism. The ram mechanism was positioned to cover the bases of the cans so that each downward stroke of the ram would actuate the cans causing them to fire simultaneously into the exposure chamber.

Each rodent was held in an individual, tapered, polycarbonate restraint tube, fitted onto the exposure chamber and sealed by means of a push fit through a rubber 'O' ring. Only the animal's nose was exposed to the test atmosphere.

Animals were observed both during and following dosing for clinical signs of drug effect.

Non-Rodent Inhalation Exposure Procedure

Inhalation dosing to Beagle dogs was performed using a dosing apparatus, comprising a mouthpiece, face mask, and modified MDI. The mouthpiece was located inside the animal's mouth on top of the tongue, and the face mask, incorporating the mouthpiece, sealed around the dog's snout by means of a rubber sleeve. The mask was connected via a one-way flap valve and exhaust tube to an extract system. The modified MDI was attached by a push fit connection to the distal end of the mouthpiece.

When assembled and fitted to the dog the animals' respiratory cycle was clearly indicated by the movement of the one-way flap valve. The MDI can was actuated manually in the normal way, by downward pressure at a time to coincide with inspiration.

Non-Rodent Intranasal Exposure Procedure

Animals were dosed by direct application of the test material into each nostril by means of an adaptor fitted to the MDI.

Results

Rodents

Fentanyl citrate in formulation of Example 3

Single Exposure Period

Using six cans firing at six shots per minute for a single-exposure period between three and ten minutes, the animals showed gradual sedation and eventually exhibited marked narcosis by ten minutes.

Multiple exposure period

Using six cans firing at six shots per minute for three ten minute exposures daily for up to five days, marked narcosis or sedation was observed for all animals for up to two hours post exposure (see Table 1).

Diamorphine hydrochloride

Using six cans firing at six shots per minute for a single-exposure period between ten and fifteen minutes, no overt pharmacological effects were noted. Animals showed a slight reduction in respiratory rate during exposure and slight salivation following exposure for a short time. Post exposure animals were slightly subdued.

Morphine sulphate

Animals were exposed to an atmosphere generated from six cans actuated at a rate of six shots per minute for a period of ten or sixty minutes. There was no observable effect seen in the behaviour of the animals following the ten minute exposure. During the second exposure, the rate of respiration dropped and following exposure the animals appeared to be very slightly subdued and easily startled.

Non-Rodent

Fentanyl citrate in Formulation of Example 3

Single exposure

Administration of test material was performed, by the inhalation and intranasal routes. Doses administered ranged from 8 to 25 actuations per session for the inhalation administration and from 5 to 35 actuations per session for the intranasal route of administration. Following inhalation, fentanyl citrate caused rapid and marked sedation with the effect lasting for at least one hour at high doses. Similar observations were seen following intranasal administration.

Multiple-exposure period

Animals were treated with a nominal dose of 0.13mg.kg fentanyl three times daily over a five day period. To achieve the correct dose, animals were weighed daily, and the body weight used to calculate the requisite number of metered dose aerosol actuations to be administered. (Results are shown in Table 2).

Diamorphine hydrochloride

A nominal dose of 30mg diamorphine hydrochloride administered by the inhalation route caused sedation in 1 out of 2 dogs. However, subsequent administration of the high dose formulation at similar or higher nominal doses, failed to produce signs of sedation in either animal. In subsequent experiments a nominal dose of 8 - 9 mg/Kg diamorphine hydrochloride administered intranasally, was capable of producing a marked degree of sedation in dogs whilst a nominal dose of 10 - 13 mg/Kg administered over three sessions caused a constant state of sedation throughout the whole dosing period.

Morphine base

Animals appeared normal following inhalation of a nominal dose of 6.5 mg/Kg. Clear signs of sedation were noted after a nominal dose of 13.0 mg/Kg was administered. These signs persisted for at least two hours. No drug related effects were seen following intranasal administration of 225 actuations over a 35 minute period.

Morphine sulphate

A total daily dose of 450 actuations of the lower concentration formulation were administered by the intranasal route. Minimal drug-related clinical signs were observed during and following treatment. Up to 330 actuations of the higher concentration formulation were also administered intranasally. At the higher dose, animals exhibited a reduced pupillary constriction on reflex to a light stimulus, became subdued and slightly sedated.

Fentanyl citrate has been demonstrated in two animal models to be a highly potent, quick acting compound with pharmacological actions persisting for about two hours.

These properties make it a good candidate for developing into a patient controlled analgesia dosage form for administration via the inhalation route. Morphine base and Morphine sulphate preparations did not show a suitable rapid onset of action, and were considerably less potent by the inhalation route than might have been expected from the intravenous dosing data.

TABLE 1

Fentanyl Citrate: Inhalation Tolerance Study in Rats - Clinical Signs

Clinical Signs Observed	Day/Dose Session/Number of Animals Affected														
	Day 1			Day 2			Day 3			Day 4			Day 5		
	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
<u>During Exposure</u>:															
Reduction in Respiratory Rate	5M/5F	5M/5F	5M/5F	5M/5F	5M/5F	5M/5F	5M/5F	5M/5F	5M/5F	5M/5F	5M/5F	5M/5F	5M/5F	5M/5F	5M/5F
<u>Post Exposure</u>:															
+ 1 min: Narcosis	5M/5F	5M/5F	5M/5F	5M/5F	5M/5F	5M/5F	5M/5F	4M/4F	5M/5F	5M/5F	5M/5F	4M/3F	5M/5F	5M/4F	3M/2F
Sedated	-	-	-	-	-	-	-	1M/1F	-	-	-	-	-	-/1F	2M/3F
+30 min: Narcosis	5M/5F	5M/5F	5M/5F	3M/5F	5M/5F	-/1F	5M/5F	1M/2F	-	2M/1F	1M/1F	1M/2F	2M/2F	2M/1F	1M/1F
Sedated	-	-	-	2M/-	-	5M/4F	-	4M/3F	5M/5F	3M/4F	4M/4F	4M/3F	3M/3F	3M/4F	4M/4F
+ 1 h : Narcosis	5M/5F	5M/5F	5M/5F	1M/1F	1M/2F	-	-	-	-	1M/1F	-	-	1M/1F	-	-
Sedated	-	-	-	4M/4F	4M/3F	5M/5F	5M/5F	5M/5F	5M/5F	4M/4F	5M/5F	5M/5F	4M/4F	5M/5F	5M/5F
+ 2 h : Narcosis	5M/5F	1M/2F	-	1M/1F	-	-	-	-	-	-	-	-	-	-	-
Sedated	-	4M/3F	5M/5F	4M/4F	5M/5F	5M/5F	5M/5F	5M/5F	5M/5F	5M/5F	5M/5F	5M/5F	5M/5F	5M/5F	5M/5F
Aggressive behaviour noted when animals returned to group cage at end of each dosing day. This lasted for approximately 30 minutes.															

Note: to facilitate ease of clinical signs observation, the animals were placed singly in cages following each dose session.

min = minutes h = hours Narcosis = unconscious Sedated = reduced activity M = male F = female

TABLE 2

Fentanyl Citrate: Inhalation Tolerance Study in Dogs - Clinical Signs

Clinical Signs Observed	Day/Dose Session																	
	Day 1			Day 2			Day 3			Day 4			Day 5					
	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3			
	M F	M F	M F	M F	M F	M F	M F	M F	M F	M F	M F	M F	M F	M F	M F	M F	M F	M F
Predose:																		
NAD	M F	M F	M F	M F	M F	M F	M F	M F	M F	M F	M F	M F	M F	M F	M F	M F	M F	M F
Sedated	– –	– –	– –	– –	– –	– –	– –	– –	– –	– –	– –	– –	– –	– –	– –	– –	– –	– –
During Dosing:																		
NAD	– –	M –	M F	– –	– –	M F	M F	M F	M F	– –	M –	M –	M –	M F	M F			
Slightly sedated	M –	– –	– –	– –	– –	– –	– –	– –	– –	– –	– –	– –	– –	– –	– –			
Ataxic	M –	– –	– –	– –	– –	– –	– –	– –	– –	– –	– –	– –	– –	– –	– –			
Tending to sit	– –	– –	– –	– –	– –	– –	– –	– –	– –	– –	– –	– –	– –	– –	– –			
Salivation	M F	– F	– –	M F	M F	– –	– –	– –	– –	M F	– F	– F	– F	– –	– –			
Vocalising	– F	– –	– –	– –	– –	– –	– –	– –	– –	– –	– –	– –	– –	– –	– –			
Heart Rate (I/D)	– –	– –	– –	– –	– –	– –	– –	– –	– –	– –	– –	– –	– –	– –	– –			
Respiration (I/D)	– –	– –	– –	– –	– –	– –	– –	– –	– –	– –	– –	– –	– –	– –	– –			
Post Dose:																		
Tending to sit	– F	– F	– F	M F	M F	– F	– F	– F	– –	– F	– F	– –	– –	– –	– –			
Crouched walk	– –	– –	– F	– –	– –	– F	– –	– F	– –	– –	– –	– F	– –	– –	– F			
Urination/ defaecation	– –	– F	– –	– –	– –	– –	– –	– –	– –	– –	– –	– –	– –	– –	– –			
Salivation	– –	– –	– –	– –	– –	– –	M F	M –	– –	M –	– –	– –	M F	– F	M F			
Ataxic	M –	M –	– F	M –	M –	M –	M –	M –	M –	M –	– –	M –	– –	– –	M F			
Sedated	M –	M –	M F	M –	M –	M –	M –	– F	M –	M –	M –	M –	M –	M –	M F			
Vocalising	– F	M F	M F	M F	M F	M F	M F	M F	M F	M F	M F	M F	– –	– F	– F			
Pinpoint pupil	– –	– –	– –	– –	– –	– –	– –	– –	– –	– –	– –	– –	M –	M –	– –			
Heart rate (I/D)	– FD	MD –	MD –	MD FD	MD FD	MD –	– –	– –	MD –	MD –	MD –	MD –	– –	– –	– –			
Respiration I/D)	– FI	MD –	MD FI	MD FI	MD –	– FI	MD –	– –	– –	MD –	– –	– –	– FI	– –	– –			

I = Increased D = Decreased M = Male F = Female

Note: both animals generally recovered ca 1 hour after each dose session

CLAIMS

1. An aerosol formulation comprising fentanyl or a physiologically acceptable derivative thereof dispersed or dissolved in an aerosol propellant.

2. An aerosol formulation as claimed in Claim 1 comprising fentanyl citrate.

3. An aerosol formulation as claimed in Claim 1 or Claim 2 in which fentanyl or a physiologically acceptable derivative thereof is present in an amount of from 0.05% to 1.0% by weight of the total composition.

4. An aerosol formulation as claimed in any preceding claim which additionally comprises a solvent for fentanyl in an amount within the range from 5 to 25% by weight based on the total composition.

5. An aerosol formulation as claimed in any preceding claim which additionally comprises a surface active agent, in which the weight ratio of surface active agent to fentanyl is in the range 1 : 100 to 10 : 1.

6. An aerosol formulation as claimed in Claim 5 in which the surface active agent is selected from sorbitan trioleate, oleic acid, lecithin and fluorinated surfactants.

7. An aerosol formulation as claimed in any preceding claim which comprises one or more of the following propellants at a concentration within the following range:

from 15 to 25% by weight Propellant 11,
from 50 to 90% by weight Propellant 12, and,
from 5 to 50% by weight Propellant 22.

8. An aerosol composition as claimed in any one of Claims 1 to 6 in which the aerosol propellant comprises 1,1,1,2-tetrafluoroethane, which is present in an amount of at least 50% by weight of the formulation.

9. An aerosol composition as claimed in Claim 8 which comprises 1,1,1,2-tetrafluoroethane, a surface active agent and at least one adjuvant having a polarity higher than 1,1,1,2-tetrafluoroethane, in which the weight ratio of 1,1,1,2-tetrafluoroethane: compound of higher polarity is in the range 50 : 50 to 99 : 1.

10. An aerosol formulation as claimed in Claim 9 in which the compound having a higher polarity is selected from ethyl alcohol, isopropyl alcohol, n-pentane, isopentane, neopentane, and mixtures thereof.

11. An aerosol composition as claimed in Claim 8 in which the fentanyl or physiologically acceptable derivative thereof is in the form of a finely divided solid material coated with a surface-active dispersing agent which constitutes at least 0.001% by weight of the coated solid material, and is suspended in an aerosol propellant comprising 1,1,1,2-tetrafluoroethane and optionally an adjuvant having a polarity equal to or less than that of 1,1,1,2-tetrafluoroethane.

12. An aerosol formulation as claimed in Claim 11 in which the finely-divided solid material constitutes up to 10.0 percent by weight of the total composition and the surface-active dispersing agent constitutes between 0.01 and 1.0 percent by weight of the finely-divided solid material.

13. An aerosol formulation as claimed in Claim 11 or Claim 12 in which the surface-active dispersing agent is selected from perfluorinated sulfonamide alcohol phosphate esters and their salts; perfluorinated alcohol phosphate ester free acids and their salts; perfluorinated alkyl sulfonamide alkylene quaternary ammonium salts; N,N-(carboxyl-substituted lower alkyl) perfluorinated alkyl sulfonamides and their salts; and mixtures thereof.

14. An aerosol formulation as claimed in any one of Claims 11 to 13 in which the propellant system comprises a mixture of 1,1,1,2-tetrafluoroethane and an adjuvant selected from perfluoropropane, perfluorobutane, octafluorocyclobutane, perfluoropentane, perfluorohexane, perfluorotributylamine, perfluoromethylcyclohexane and perfluorodecalin.

15. A pressurised aerosol inhaler comprising a container containing an aerosol formulation as claimed in any preceding claim and a valve capable of dispensing doses of formulation.

16. A pressurised aerosol inhaler as claimed in Claim 15 additionally comprising control means to control the dosing frequency from the valve.

17. A pressurised aerosol inhaler as claimed in Claim 16 in which the control means is constructed and arranged such that not more than a predetermined maximum number of doses may be dispensed within a set period of time.

Fig.1.

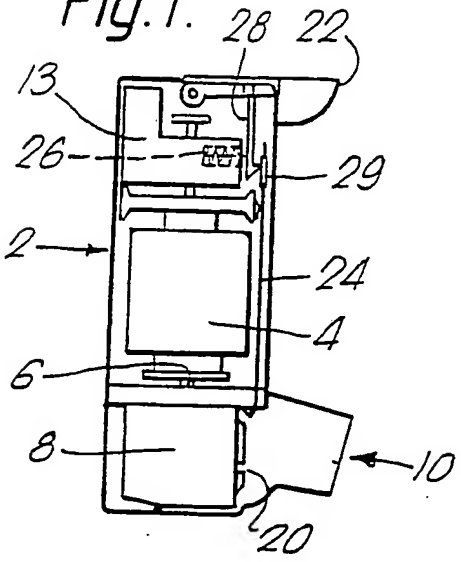
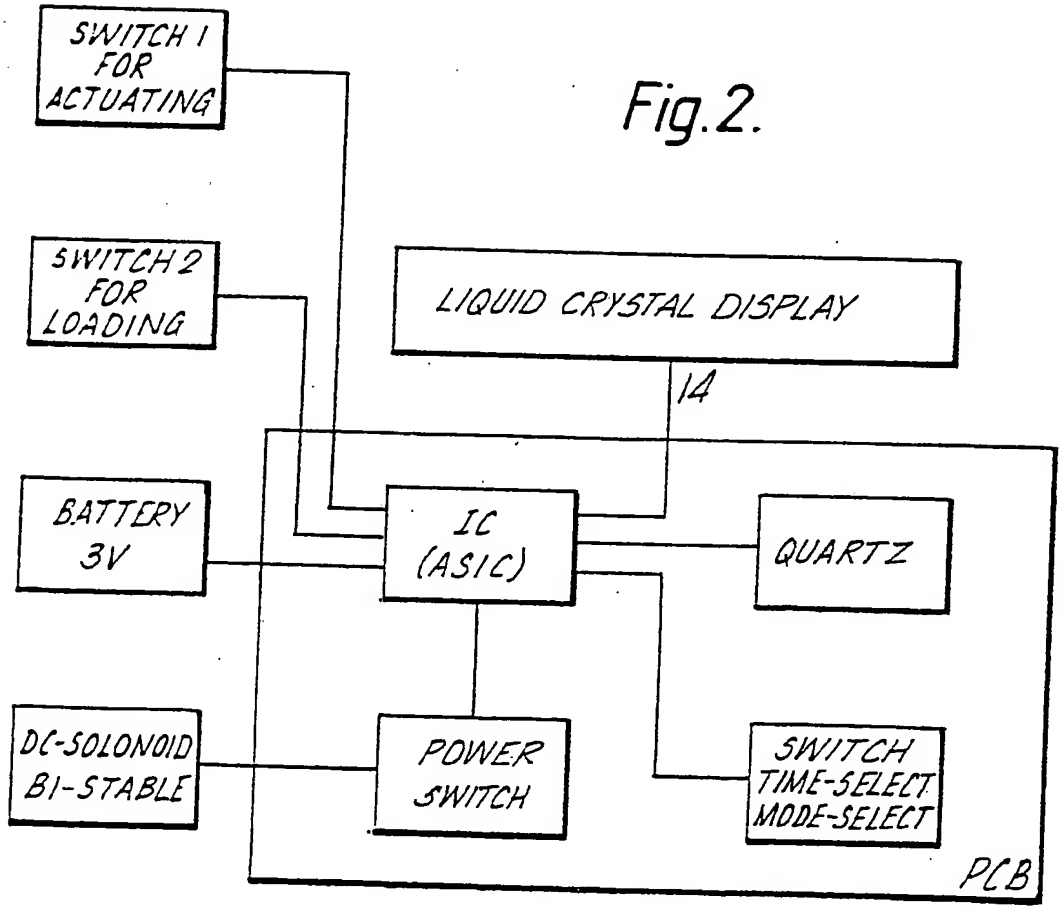


Fig.2.



INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 90/00015

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[5]: A 61 K 31/445, A 61 K 9/12, A 61 K 9/72

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System [8]	Classification Symbols
IPC[5]	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [9]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	DE, A, 3602370 (S. CHRUBASIK) 6 August 1987 see claims 1-5; column 2, lines 31-32	1-2

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* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
30th March 1990	20 AVR. 1990
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	MISS T TAZELAAR

Form PCT/ISA/210 (second sheet) (January 1985)

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 9000015

SA 33422

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 17/04/90
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE-A- 3602370	06-08-87	None	

EPO FORM P0139

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82